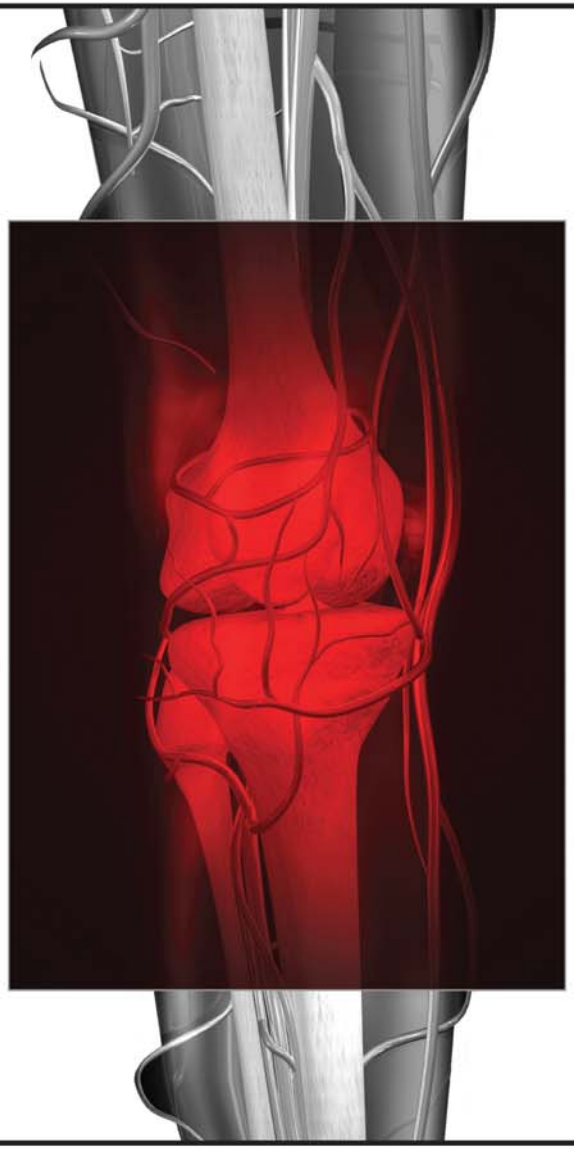


# Pain Management in the Era of NSAID Controversies

## Canadian Pain Society's Annual Conference

May 30, 2008 • 7:30 – 8:30 am
Breakfast Symposium
Victoria Conference Centre
Salon B and C, Level 2

JANSSEN-ORTHO

the CANADIAN PAIN SOCIETY
la SOCIÉTÉ CANADIENNE de la DOULEUR

# Pain Management in the Era of NSAID Controversies

Dr. Sol Stern

Chair

# Touchpad System

# Where are you from?

1. Atlantic
2. Quebec
3. Ontario
4. West
5. International

# What is your practice area?

1. Family Physician
2. Specialist Physician
3. Registered Nurse
4. Physiotherapist
5. Rheumatologist
6. None of the above

# Pain Management in the Era of NSAID Controversies

Dr. Philip A. Baer
Canadian Pain Society
May 2008

# Disclosure

Speaker, Advisory Boards, Investigator:

Janssen-Ortho

Paladin, Biovail, Purdue

Merck, Pfizer, Procter & Gamble

Sanofi-Aventis, Lilly, Novartis

Abbott, Amgen, Wyeth, Schering

Roche, Bristol Myers Squibb

"Off-label uses of medications may be discussed during this presentation."

# Educational objectives

- To review Canadian pain statistics
- To better understand the potential adverse effects of nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors (COXIBs)
- To review the most recent guidelines on musculoskeletal pain management
- To discuss the management of musculoskeletal pain, including the role of opioids such as tramadol

# Pain: Understanding and Challenges for the Rheumatologist

- "To date, pharmacologic treatments, such as simple analgesics and NSAIDs, have been the main focus of rheumatology pain management. Rheumatologists, in general, are not experienced in the management of chronic pain beyond this simple paradigm."

Fitzcharles MA et al. Arthritis Rheum 2005; 52: 3685


*Selling or carrying coal to Newcastle* is an idiom of British origin describing a foolhardy or pointless action

# Review of Canadian Pain Statistics

# Canadian Chronic Pain Study II (CCPS II) 2007 Summary

What percentage of the Canadian population suffers from chronic pain?

1. 6 %
2. 12 %
3. 17 %
4. 25 %

**CCPS II:**

- Prevalence increases with age (17% - 33%)
- Higher in women (27% vs 22%)
- Present for at least 9 years and of moderate intensity
- Arthritic conditions are the #1 reason (31%)
- Low back/spinal conditions are #2 (21%)
- > 60% of MDs and patients thought moderate to severe chronic pain was not well treated

Boulanger A et al, PR&M, Vol 12 No 1, 2007

# Case Study

# Case Study (1): Victoria

- 62 year old woman, retired teacher
- Osteoarthritis both hips
- Limited walking, dressing
- Using cane
- Looking after disabled husband; not in a position to consider surgery
- Persistent pain 3-6/10; fluctuates with activity
- Sleeps well

# Case Study (2): Victoria

- PMH: mild CHF with prior MI, peptic ulcer
- Current issues:  Diabetes, hypertension, BMI 29, eGFR 45
- Meds: metformin, ECASA, ACEI, diuretic
- Prior unsuccessful OA therapies:
  - Acetaminophen 3500 mg/day
  - Tylenol® #3 six tablets/day:  constipation
  - tNSAID:  increased blood pressure
  - Physiotherapy
  - Glucosamine and chondroitin

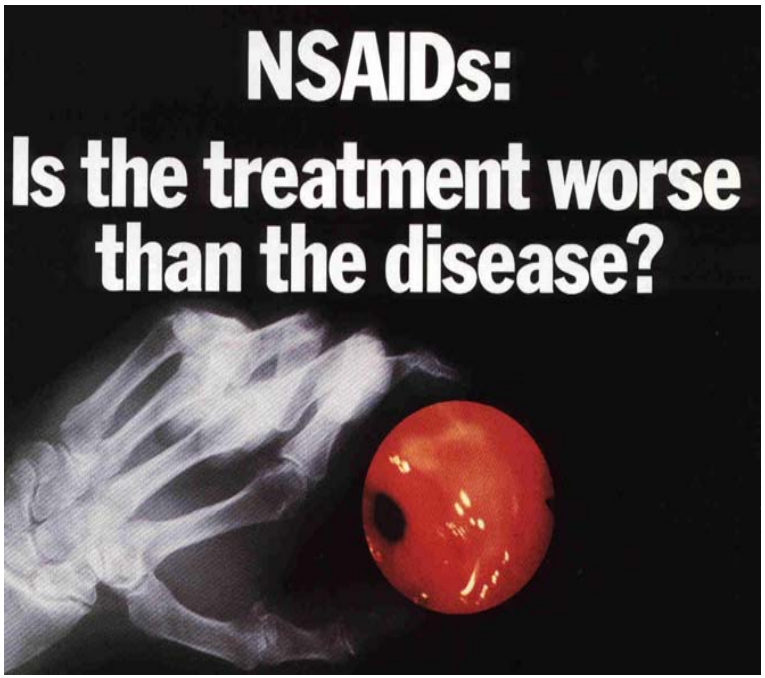
PMH = Past Medical History; CHF = Congestive Heart Failure; MI = Myocardial Infarction; DM = Diabetes Mellitus; BP = Blood pressure; BMI = Body Mass Index; eGFR = estimated glomerular filtration rate; ECASA = enteric-coated acetylsalicylic acid; ACEI = Angiotensin-Converting enzyme inhibitor; tNSAID = Traditional nonsteroidal anti-inflammatory drug

# Assuming You Have Maximized Nonpharmacological Treatments, What Medication Would You Prescribe to Help Reduce Her Pain and Improve Her Quality of Life?

1. NSAIDs/Coxibs (eg celecoxib, naproxen)
2. Typical opioids (eg oxycodone, morphine)
3. Intra-articular steroid injections
4. Atypical opioids (eg tramadol)

Coxibs = Cyclooxygenase 2 inhibitors

# Issues With NSAIDs/Coxibs



# NSAIDs: Perspectives

Recommendations:

- Patients should be fully informed about evolving information regarding the benefits and risks of their treatment options.

- NSAIDs/Coxibs should be used with caution in elderly patients, who are at greatest risk for serious gastrointestinal (GI), renal, and cardiovascular side effects.

An Evidence-Based Approach to Prescribing NSAIDs
The Third Canadian Consensus Conference

Tannenbaum H, et al. J Rheumatol 2006;33:140

September 26, 2006

- All NSAIDs and cyclooxygenase -2 (COX-2) inhibitors can cause or worsen hypertension, CHF, edema, and impaired kidney function

- Most NSAIDs and COX-2 inhibitors pose similar increased risks of heart attack

# Health Canada Warnings and Precautions NSAID/Coxib Class Labelling

## Risk of Cardiovascular (CV) Adverse Events: Ischaemic Heart Disease (IHD), Cerebrovascular Disease (CVD), CHF (NYHA II-IV)

"Use of some NSAIDs is associated with an increased incidence of CV adverse events which can be fatal"

"Caution should be exercised in prescribing... to any patient with: IHD, CVD and/or CHF (NYHA II-IV)"

"Use of NSAIDs, such as... can promote Na+ retention in a dose-dependent manner which can result in increased blood pressure and/or exacerbation of CHF"

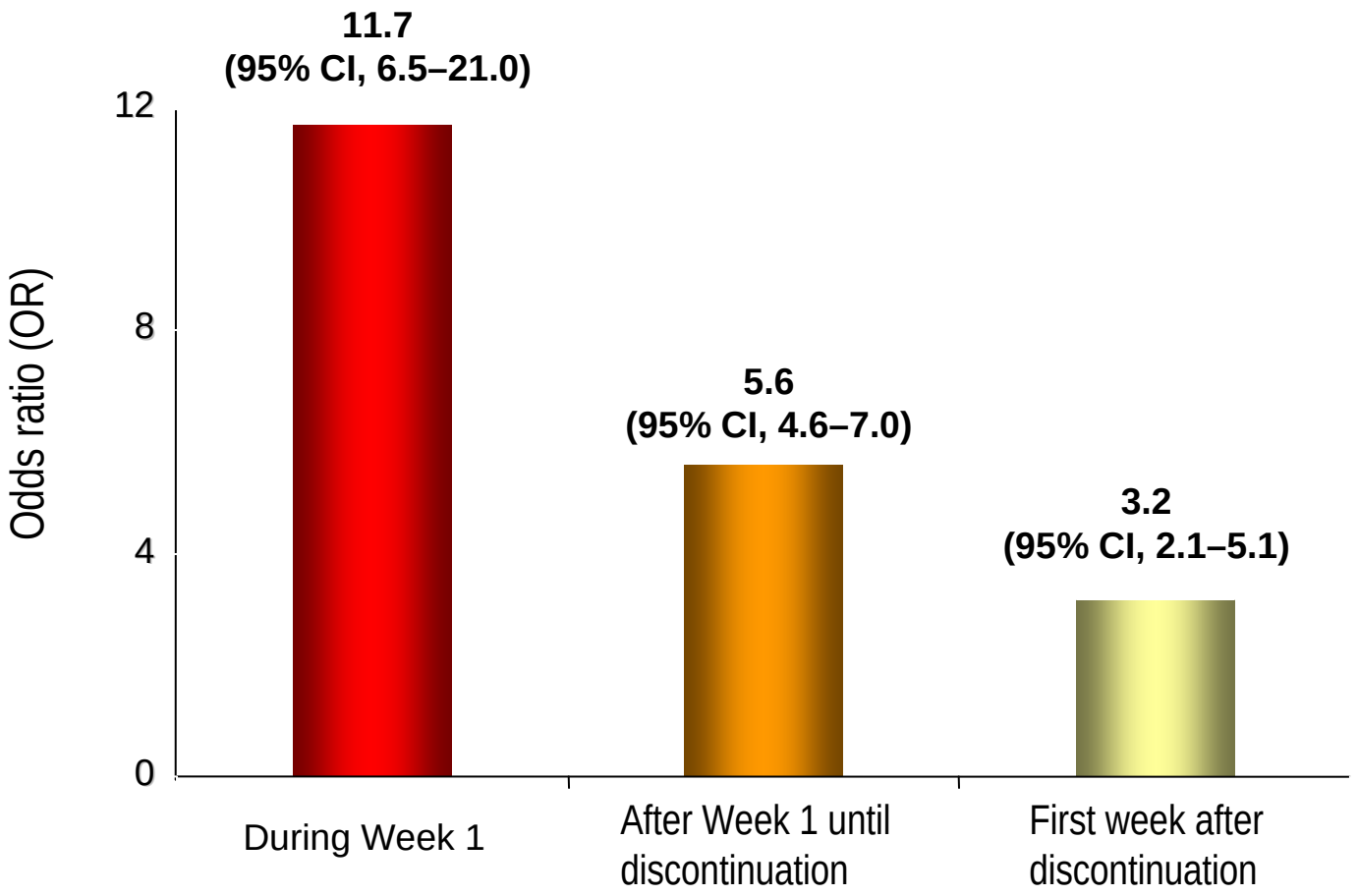
"Randomized clinical trials with... have not been designed to detect differences in CV events in a chronic setting. Therefore, caution should be exercised when prescribing..."

Health Canada Basic Product Monograph on Information for Nonsteroidal Anti-Inflammatory Drugs (NSAIDs); 2006/10/04

# What Period Is Associated With the Highest Risk of Serious GI Complications When Taking an NSAID?

1. The first 7 days
2. The first 14 days
3. The first 30 days
4. The period after the first 6 weeks of therapy

# Risk of NSAID-Induced GI Bleeding and Duration of Use




Lewis SC, et al. *Br J Clin Pharmacol* 2002;54:320

# Risk Factors for NSAID-Associated Serious GI Adverse Events

| Characteristic | Odds Ratio (95% Interval) |
|---|---|
| History of ulcer complications | 13.5 (10.3-17.7) |
| Multiple NSAIDs | 9.0 (5.7-14.2) |
| High-Dose NSAIDs | 7.0 (5.2-9.6) |
| Concomitant anticoagulant use | 6.4 (2.8-14.6) |
| Age > 70 years | 5.6 (4.6-6.9) |
| Age > 60 years | 3.1 (2.5-3.7) |
| Concomitant corticosteroid use | 2.2 (1.4-3.5) |
| History of CVD | 1.8 (1.1-3.2) |

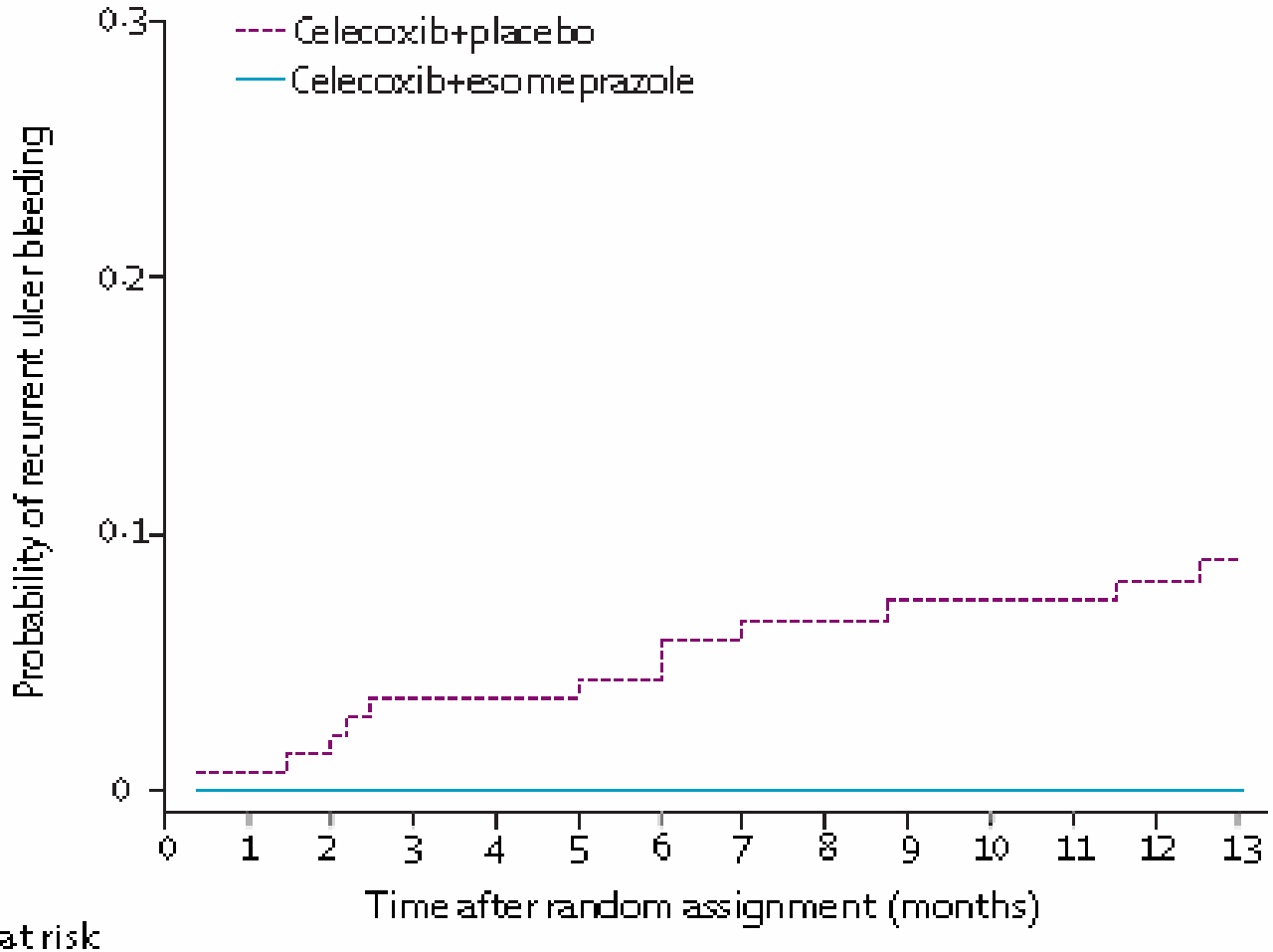
Adapted from Hunt RH et al. Recommendations for the appropriate use of anti-inflammatory drugs in the era of the coxibs: defining the role of gastroprotective agents. Can J Gastroenterol. 2002 Apr;16(4):231-40. Review.

# Absolute GI Safety: Coxib + Proton Pump Inhibitor (PPI)

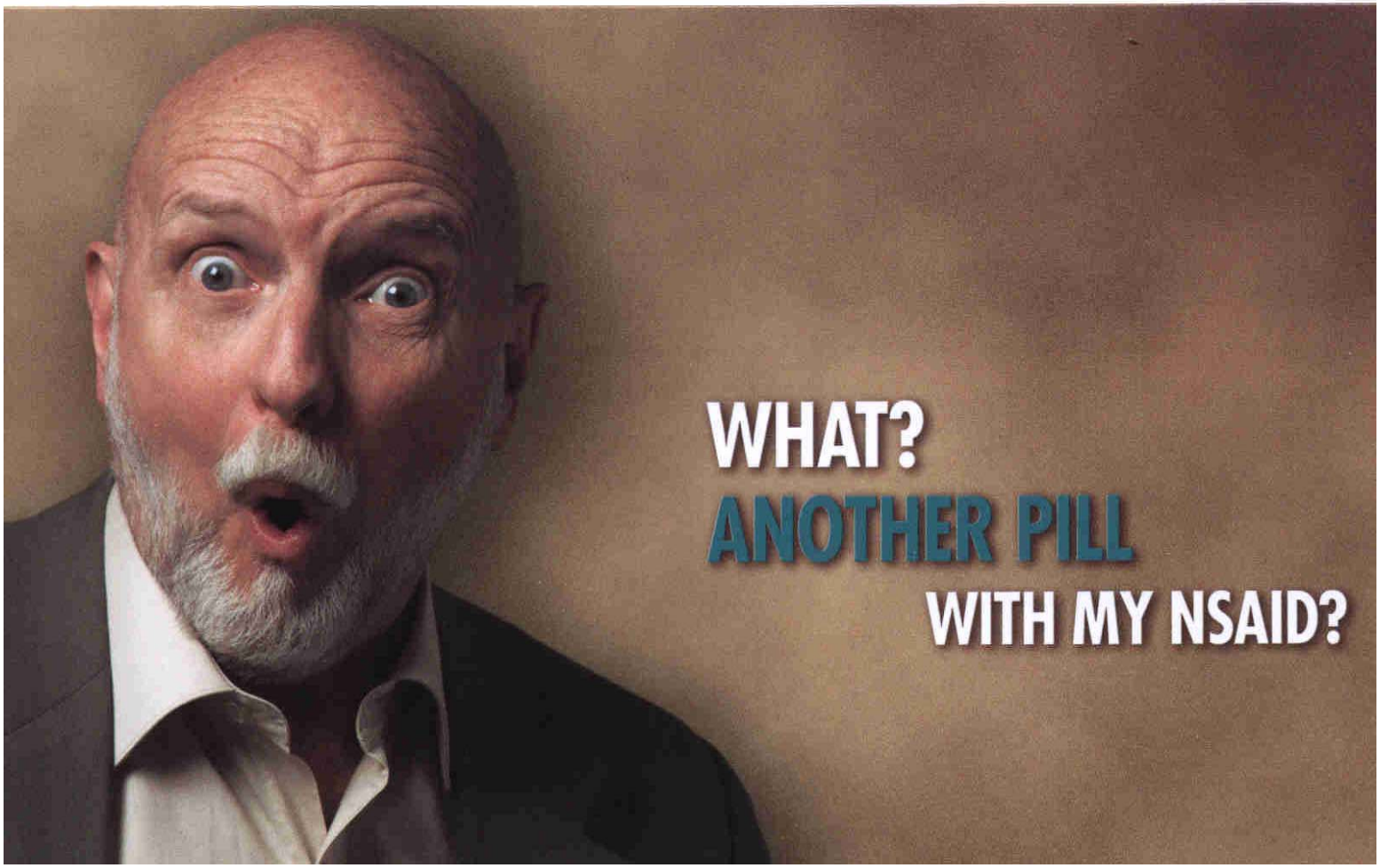
Celecoxib 200 mg BID

+/-

Esomeprazole 20 mg BID




| Number at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Celecoxib with esomeprazole | 137 | 136 | 136 | 136 | 136 | 135 | 135 | 135 |
| Celecoxib with placebo | 136 | 132 | 130 | 127 | 125 | 124 | 123 | 122 |


WHAT?
ANOTHER PILL
WITH MY NSAID?

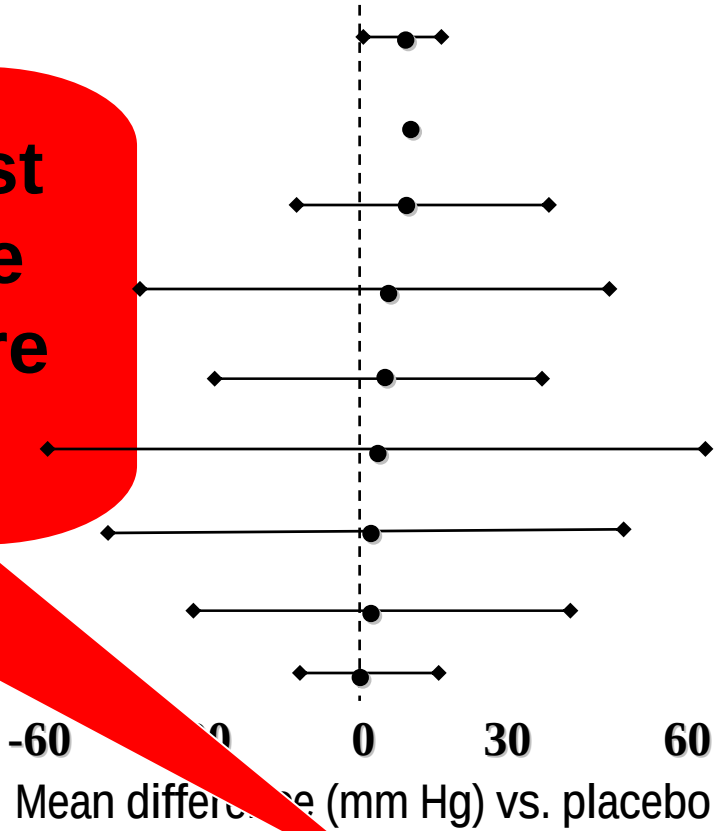
# NSAIDs/Coxibs and GFR

- GFR > 60 ml/min: OK to use
- GFR 30-60 ml/min: Use with caution and careful monitoring
  - Weight
  - Blood pressure
  - Electrolytes
  - Creatinine, eGFR
- GFR < 30 ml/min: Don’t use

# Hypertension With NSAIDs

| Drugs | n | Trials |
|---|---|---|
| Piroxicam | 27 | 4 |
| | | |
| | | |
| | | |
| | | |
| Sulindac | 85 | 7 |
| Aspirin | 105 | 8 |

**“Our results suggest that NSAIDs elevate mean blood pressure by 5 mm Hg…”**




Johnson AG,et al. (1994). *Ann Intern Med*, 1994; 121:289

# CV Risk of NSAIDs/Coxibs

Risk of a CV event
(MI / CVA / Sudden death)

COX-2: placebo 1.42
COX-2: NSAID 1.16 (NS)

Absolute ↑ risk 0.3% per year

NNH 333

CVA = Cerebrovascular accident
NS = Not significant
NNH = Number needed to harm

Kearney PM, et al. *BMJ* 2006;332;1302

# Recommendations on Arthritis Pain Management

# Modified "WHO Analgesic Ladder"

Increasing Pain

**Mild Pain**

Acetaminophen
Acetylsalicylic acid (ASA)
NSAIDs/Coxibs
(+/- adjuvants)

**Moderate Pain**

Codeine
Oxycodone
Tramadol
(+/- acetaminophen)
(+/- adjuvants)

**Severe Pain**

Fentanyl
Hydromorphone
Methadone
Morphine
Oxycodone
(+/- adjuvants)


Adapted from *The World Health Organization*, Cancer pain relief, 2nd edi., World Health Organization;

Leppert W, Luczak J.1996 *Support Care Cancer* 2005;13:5

# Management of OA (ACR)

**Diagnosis**

**Physical Measures – Patient Education**

Medications

Anti-inflammatory

Analgesic

Intra-articular

NSAID + $PGE_2$/PPI
COX-2 inhibitors
Topical NSAIDs

Acetaminophen

Steroids
Hyaluronate

Tramadol
Topicals
Opioids

Antidepressants
Glucosamine
Chondroitin

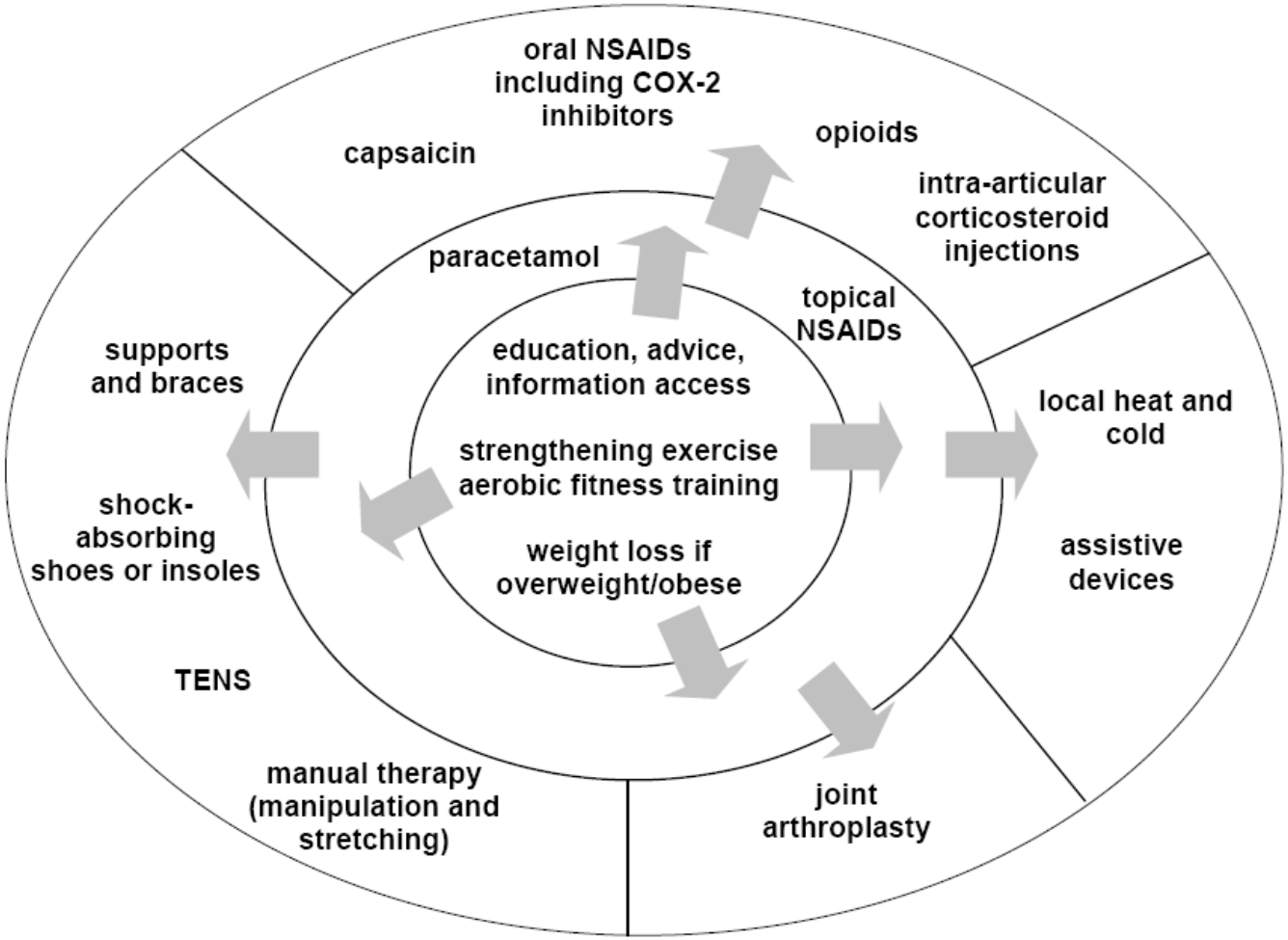
Surgery

PGE2 =Prostaglandin E2 analogue

(misoprostol)

American College of Rheumatology Subcommitte on Osteoarthritis Guidelines. *Arthritis Rheum* 2000;43:1905

# NICE OA Clinical Guideline for Care and Management in Adults




NICE = National Institute for Health and Clinical Excellence

Conaghan PG,et al, *BMJ* 2008;336:502

# Guidelines on Opioids and Tramadol for Arthritis Pain

# OARSI Guidelines 2008

- Management of Hip and Knee OA
  - # 20. The use of weak opioids and narcotic analgesics can be considered for the treatment of refractory pain in patients with hip or knee OA, where other pharmacological agents have been ineffective, or are contraindicated…
    - SOR: 82% (95% CI 74-90)

OARSI = Osteoarthritis Research Society International

*Lhang W, et al. Osteoarthritis and Cartilage* 2007;15:981

*Lhang W, et al. Osteoarthritis and Cartilage* 2008;16:137

# NICE OA Clinical Guideline for Care and Management in Adults

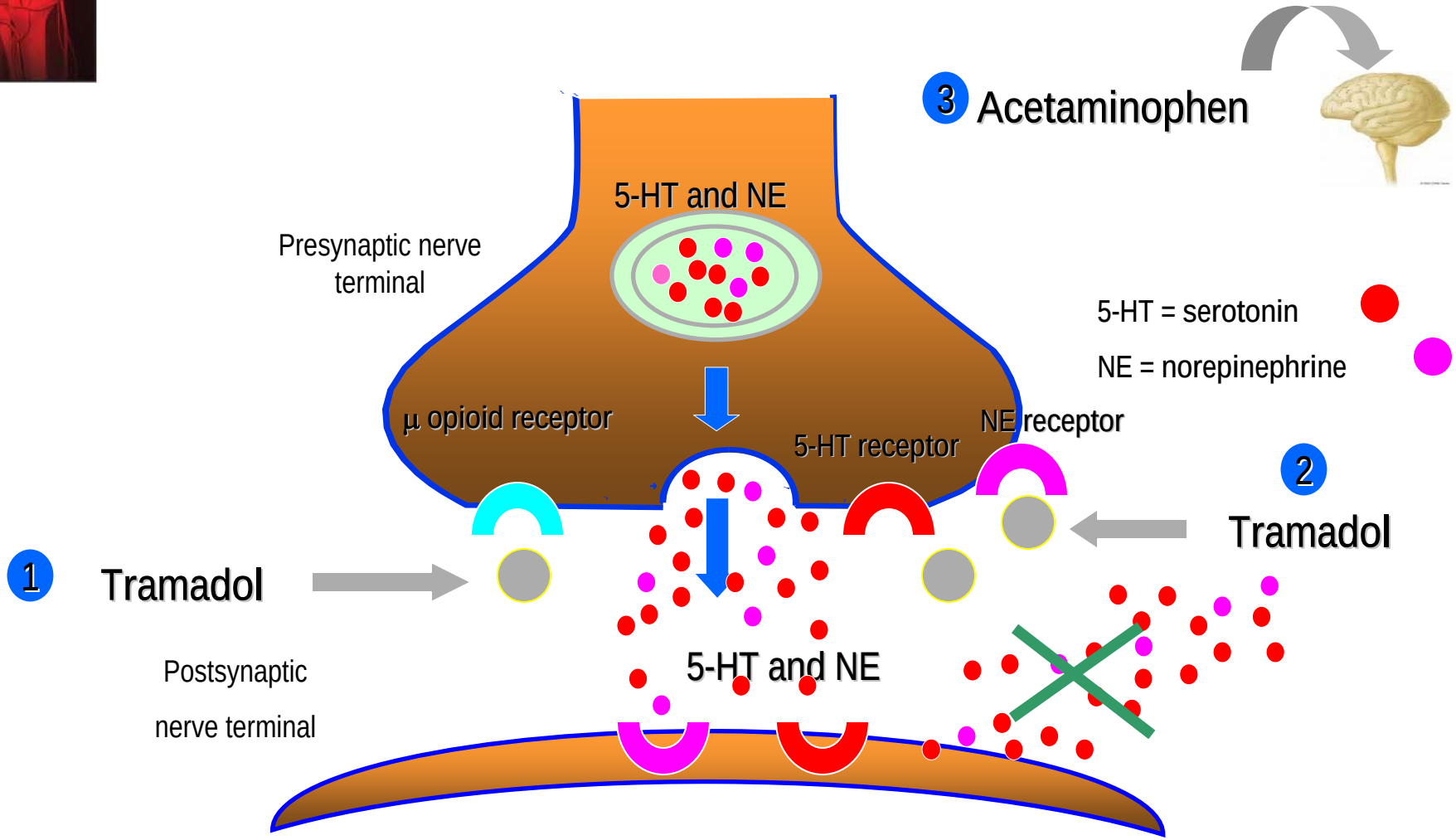
- Oral analgesics
  - If paracetamol or topical NSAIDs are insufficient for pain relief for people with osteoarthritis, *then the addition of opioid analgesics should be considered. Risks and benefits should be considered, particularly in elderly people.*

Conaghan PG,et al, *BMJ* 2008;336:502

# Tramadol Preparations (Canada)

- Tramacet®
  - Tramadol 37.5 mg / acetaminophen 325 mg
  - Indication:  moderate to moderately severe pain in adults (revised 2008)
- Once-daily tramadol preparations
  - Three preparations:  100-400 mg tablets
  - Indication:  pain of moderate severity in adults who require treatment for several days or more

# Mechanism of Action: Tramacet




1. Binding of Tramadol to μ-opioid receptor (weak agonism)
2. Inhibition of reuptake of 5-HT and NE
3. Acetaminophen: unknown mechanism of action in the CNS

# Tramacet Studies in Arthritis Pain

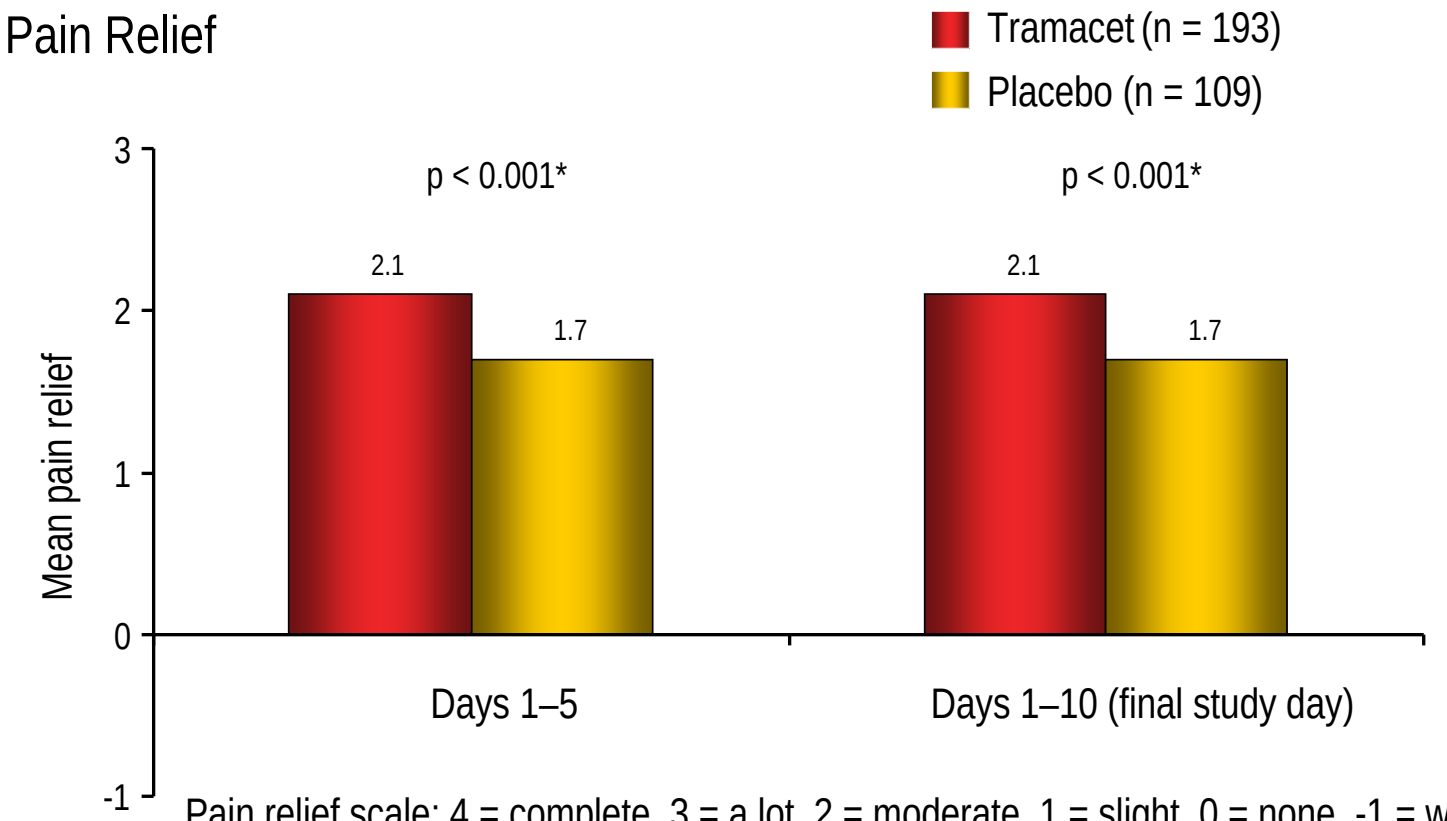
# Tramacet Acute Pain Clinical Trials

- OA flare on NSAID/Coxib
  - Tramadol/Acetaminophen vs placebo for 10 days
  - Silverfield JC, et al. *Clin Ther* 2002;24:282
  - Rosenthal NR, et al. J Am Geriatr Soc 2004;52:374

- Rheumatoid arthritis (RA) Pain on NSAID / DMARD
  - Tramadol/Acetaminophen vs placebo for 7 days
  - Lee EY, et al. *Clin Ther*. 2006;28:2052

DMARD = Disease-modifying antirheumatic drug

# OA Flare Pain: Addition of Tramacet to Anti-inflammatory




Pain relief scale: 4 = complete, 3 = a lot, 2 = moderate, 1 = slight, 0 = none, -1 = worse
*p-values based on analysis of covariance (ANCOVA) model with treatment and centre as qualitative factors, and baseline pain-intensity score as a covariate

Silverfield JC, et al. *Clin Ther* 2002;24:282. Copyright with permission.

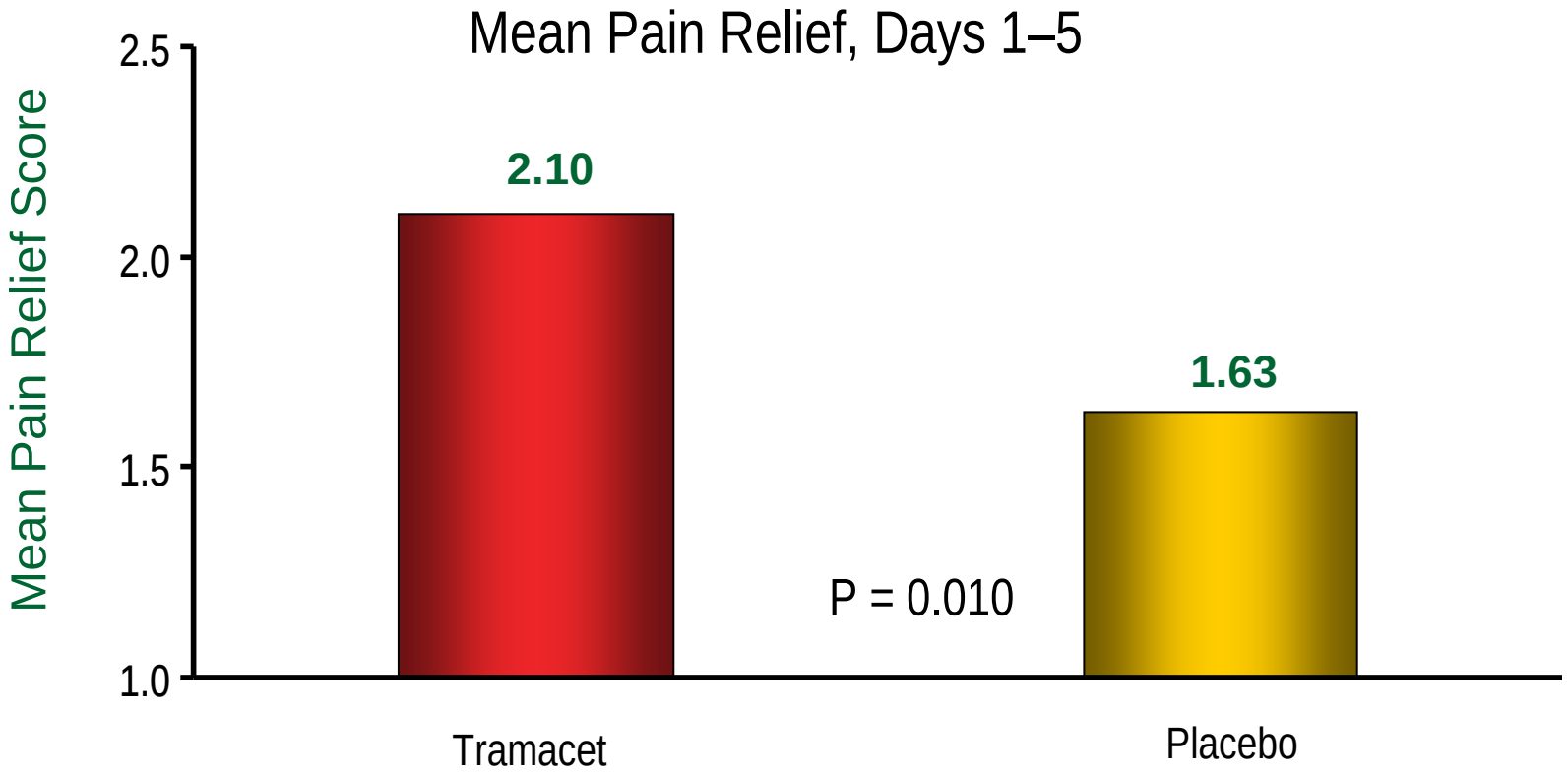
# Tramacet in OA Flare Pain: Function and Quality of Life

| Category<br>Treatment | No. of Patients | Mean (+SD) WOMAC Score* Baseline | Final | P-Value vs Placebo |
|---|---|---|---|---|
| Pain | | | | |
| Tramacet | 192 | 5.97 + 1.46 | 3.41 + 1.82 | 0.004 |
| Placebo | 110 | 6.02 + 1.36 | 4.00 + 1.91 | |
| Joint stiffness | | | | |
| Tramacet | 193 | 6.63 + 1.71 | 4.25 + 2.08 | 0.100 |
| Placebo | 110 | 6.58 + 1.88 | 4.59 + 1.99 | |
| Physical function | | | | |
| Tramacet | 193 | 5.99 + 1.45 | 3.77 + 1.76 | 0.013 |
| Placebo | 109 | 5.93 + 1.46 | 4.16 + 1.82 | |
| Overall | | | | |
| Tramacet | 193 | 6.09 + 1.35 | 3.72 + 1.70 | 0.008 |
| Placebo | 110 | 6.08 + 1.36 | 4.19 + 1.79 | |

*Western Ontario and MacMaster (WOMAC) Universities Osteoarthritis Index Questionnaire

Silverfield JC, et al. *Clin Ther* 2002;24:282

# Tramacet in OA Flare Pain (Elderly Subset)

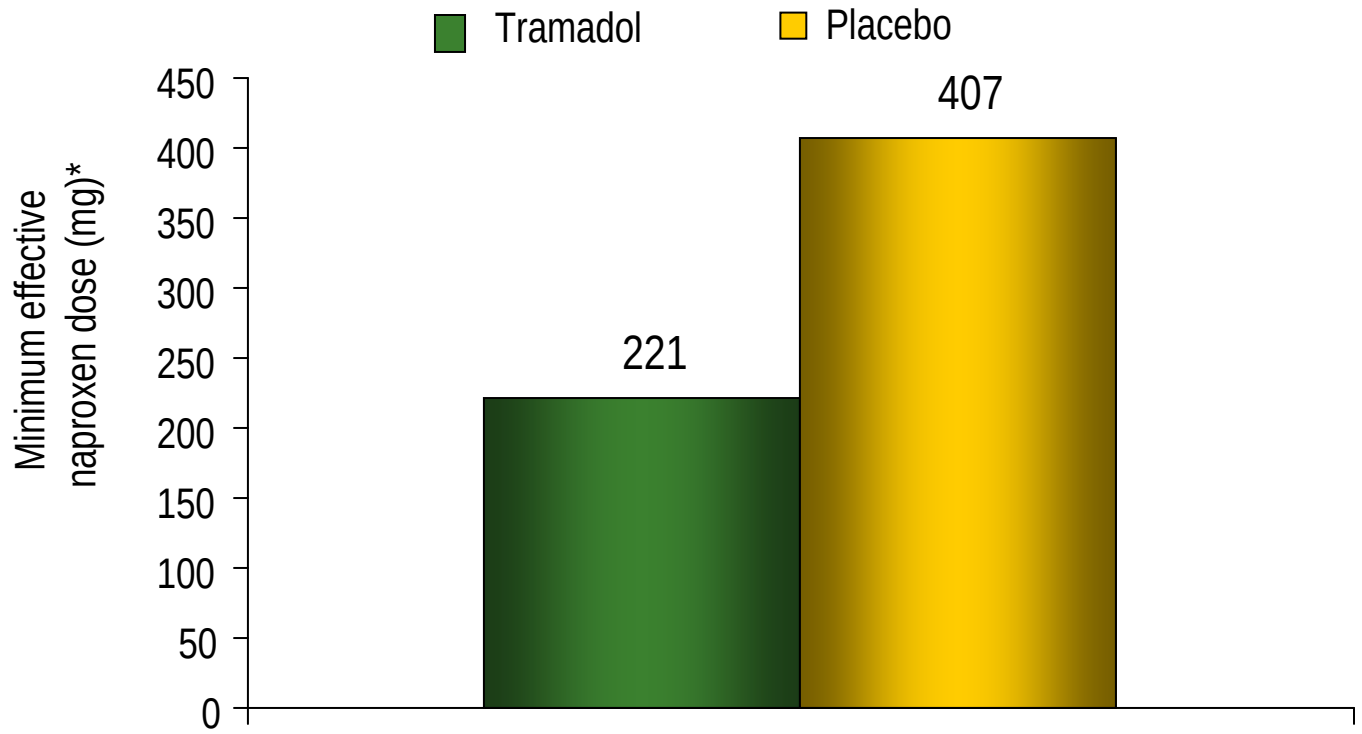



Rosenthal NR, et al. *J Am Geriatr Soc* 2004;52:374

# Tramacet Chronic Pain Clinical Trials

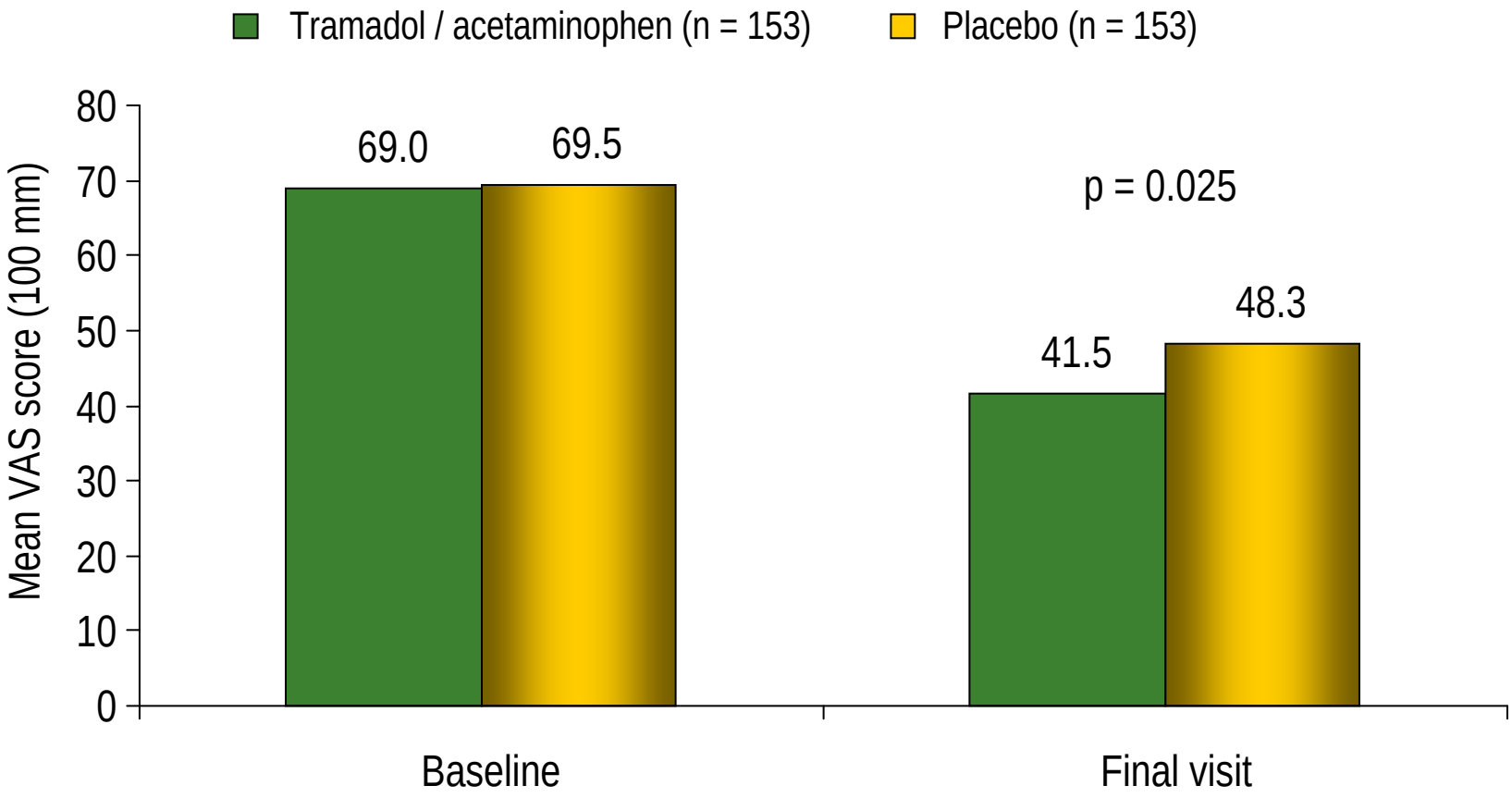
- NSAID-dose Reduction in OA
  - Tramadol IR versus placebo (Schnitzer T et al, 1999)
- Chronic Low Back Pain
  - Tramadol/acetaminophen versus placebo (Peloso PM, et al; 2004)
- Chronic Low Back and/or Osteoarthritic Pain
  - Tramadol/acetaminophen versus codeine/APAP (Mullican WS, et al; 2001)
- OA on COXIB Therapy
  - Tramadol/acetaminophen versus placebo (Emkey R, et al; 2004)
- Fibromyalgia
  - Tramadol/acetaminophen versus placebo (Bennett RM, et al; 2003 and 2005)
- Neuropathic pain
  - Tramadol/acetaminophen versus placebo (Freeman R, et al; 2007)

# Mean Minimum Effective Naproxen Dose: Naproxen Responders




Schnitzer TJ, et al. *Arthritis Rheum* 1999;42:1370-1377

# OA Pain: Tramacet Add-on to Coxibs
# Mean Daily Pain Intensity (0-91 Days)



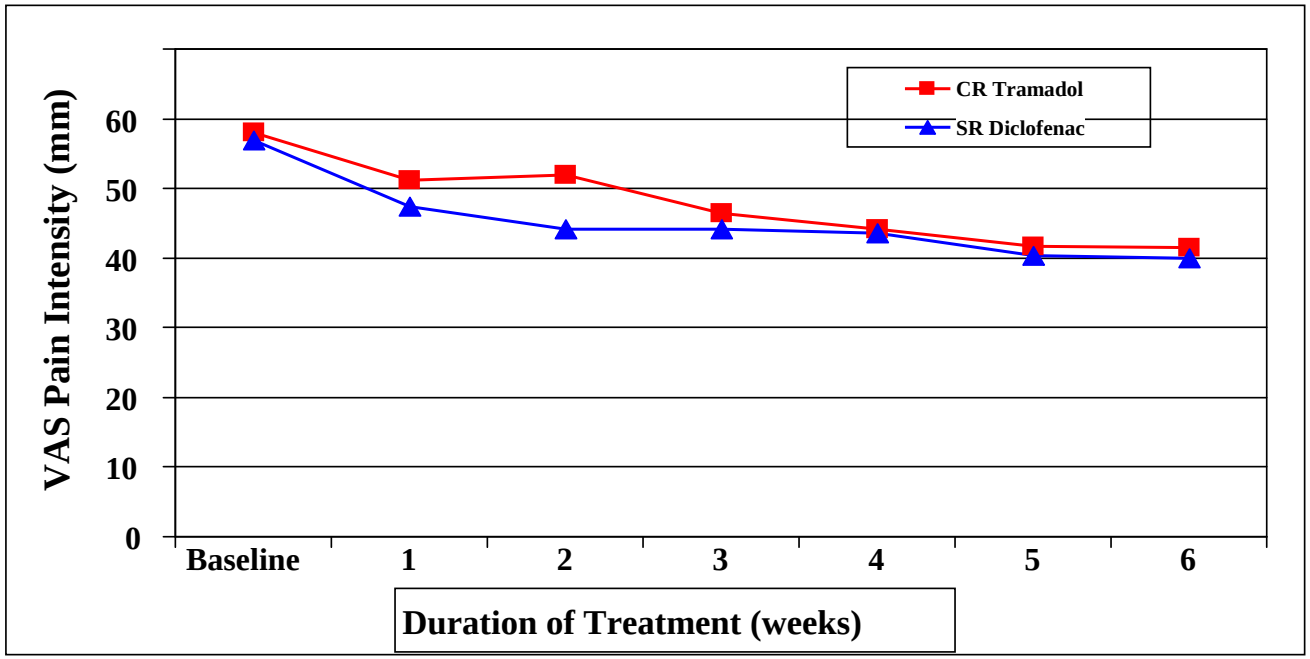

Emkey R, et al. *J Rheumatol* 2004;31:150

# Which Statement Is True Regarding the Use of Tramadol Versus NSAIDs in OA Pain?

1. Efficacy and safety are comparable
2. Tramadol has better efficacy
3. NSAIDs have better efficacy
4. Efficacy is equal, but tramadol has better safety
5. Efficacy is equal, but NSAIDs have better safety

# Tramadol Versus NSAID: OA Comparison Trial

# CR Tramadol Versus SR Diclofenac Study




- There was no difference in the overall VAS pain intensity or the WOMAC pain subscale between the two groups
- There was no difference between treatments in physical function and joint stiffness (measured by WOMAC subscales)

CR = Controlled release
SR = Sustained release

Beaulieu A, et al. *Pain Res Manage* 2008;13: 103

# CR Tramadol Versus SR Diclofenac Study (cont'd)

- Adverse effects:
  - Typical opioid-related effects such as dizziness, nausea, constipation, somnolence
  - Two patients in the SR diclofenac group hospitalized
    - One for GI bleed, one for severe pancreatitis – after 14 days
    - Both deemed related to the SR diclofenac
  - No serious adverse effects in patients in the CR tramadol group
- Conclusion:
  - CR tramadol is as effective as SR diclofenac in the treatment of pain due to OA

Beaulieu A, et al. *Pain Res Manage* 2008;13:103

# Case Study: Victoria

- 62 year old woman, retired teacher
- Osteoarthritis both hips
- Limited walking, dressing
- Using cane
- Looking after disabled husband; not in a position to consider surgery
- Persistent pain 3-6/10; fluctuates with activity
- Sleeps well

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- PMH: mild CHF with prior MI, peptic ulcer
- Current issues: Diabetes, hypertension, BMI 29, eGFR 45
- Meds: metformin, ECASA, ACEI, diuretic
- Prior unsuccessful OA therapies:
  - Acetaminophen 3500 mg/day
  - Tylenol® 3 six tablets/day: constipation
  - tNSAID:  increased blood pressure
  - Physiotherapy
  - Glucosamine and chondroitin

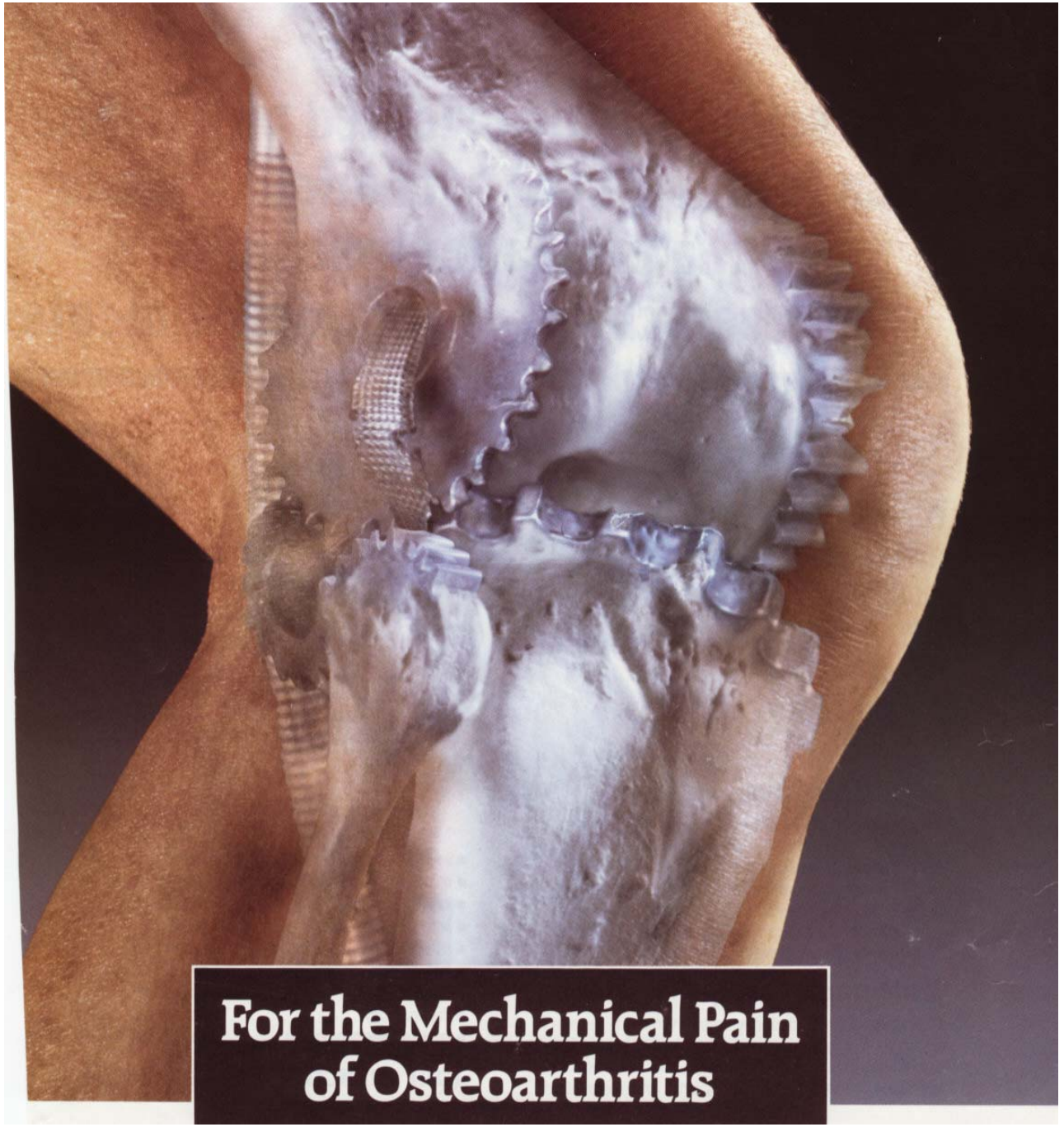
# What Would Be Your First Medication Change?

1. Increase her Tylenol® 3 to 8 tablets/day
2. Add an NSAID with a PPI
3. Add a Coxib
4. Replace her Tylenol #3 with tramadol/acetaminophen
5. Prescribe a WHO step-3 opioid

# Summary

# Common Findings in Arthritis Patients

- Older age group
- Comorbidities: Hypertension, diabetes, cardiovascular disease, decreased renal function
- Medications which increase GI risk: ASA, Selective serotonin reuptake inhibitors (SSRIs)
- Medications which increase bleeding risk: ASA, warfarin, clopidogrel


For the Mechanical Pain
of Osteoarthritis

# Osteoarthritis

- "Pain is the malady – not osteoarthritis"

**Sources of Pain in OA**

**SYNOVIUM**
> Inflammation

**BONE**
> Medullary hypertension
> Subchondral fracture

**OSTEOPHYTES**
> Periosteal reaction
> Nerve compression

**CAPSULE**
> Distension
> Instability

**MUSCLES/LIGAMENTS**
> Spasm
> Strain

**Pain drives OA treatment**

Hadler NM. *Ann Intern Med* 1992;116:598

Moskowitz RW. *The Rheumatologist* 2008;2: 14

# Questions?


“And now, my mother, Mrs Knable, will put you to sleep with tales of her arthritis.”